REMARKS

Claim 68, 85, 88, 91 and 94 have been deleted.

The limitations of claim 68 have been introduced into claim 67. Claim 69 has been made independent by incorporating the limitations of previous claims 67 and 68.

No new matter has been added.

Objections

The Examiner points out that no SEQ ID NOS for the sequences disclosed in the Specification on page 119, lines 26 and 28 are present. Applicants note that while the amendment filed on November 13, 2001 entered appropriate SEQ ID NOS for the majority of the sequences appearing in the Specification, the section on page 119, lines 26 and 28 was inadvertently omitted. Applicants have amended the Specification to include reference to SEQ ID NO. 1, which discloses the PSM sequence, thereby overcoming the objection.

The Examiner notes that the application appears to claim subject matter disclosed in co-pending application 60/105,011, but fails to make a formal claim of priority. Applicants have amended the first paragraph of the Specification to include the priority claim and to provide the status of all non-provisional parent applications, thereby overcoming the objection.

The Examiner has objected to the disclosure based on an incorrect address for the ATCC. Applicants have amended the address, providing the current address, thereby overcoming the objection.

Rejections Under USC § 103

The Examiner has rejected claims 67, 68, 84, 85, 87, 88, 90 and 91 as being obvious over US 2002/0090379A1 in view of Fendly et al. The Examiner contends that 2002/0090379A1 teaches analogues of self proteins that are made immunogenic by inserting foreign T_H cell epitopes, including those from tetanus, that are universally recognized and that such analogues may be used to treat cancer. The Examiner

acknowledges that this reference does not teach the analogue where the self-protein is human HER2.

The Examiner contends that Fendly et al. teach the human HER2/neu proto-oncogene is amplified and overexpressed in a variety of human adenocarcinomas and treatment approach is to direct the patients own immune system toward these tumor cells that over express HER2. The Examiner contends that Fendly et al. further teach that the extracellular domain of HER2 could stimulate both humoral and cellular immune responses when administered with Detox adjuvant and could inhibit growth of a breast cell tumor line that overexpressed HER2. Lastly, the Examiner alleges that Fendly et al. teach that it is conceivable that HER2-ECD given with a potent adjuvant can lead to effective immunization.

The Examiner then concludes that it would have been obvious to the skilled artisan to have made analogues of the HER2 protein taught by Fendly et al. with inserted foreign T_H epitopes as taught for the self protein analogues of 2002/0090379A1 and to have administered it to humans using the Detox adjuvant of Fendly et al. She further contends that the motivation to do this would come from the desire to treat human adenocarcinomas as taught by Fendly by directing the patients own immune system toward those tumor cells that overexpress HER2. Applicants respectfully traverse.

In general, the primary reference 2002/009037A1 deals with induction of antibodies that are reactive with self-proteins. Nothing is mentioned about the possibility of inducing anti-self cellular immunity. In contrast, the present invention relates to immunogenic analogues of HER-2 that include autologous CTL epitopes to enable an activated CTL to attack cells harboring HER2. Although the presently claimed HER-2 analogues are designed to break tolerance, they are, as clearly indicated in the Specification, primarily designed to break *CTL* tolerance, not only B-cell tolerance. This is in contrast to 2002/009037A1, which aims first and foremost at preserving B-cell epitopes, rather than the aim of the present invention to also preserve CTL epitopes.

These two objectives are not necessarily compatible when a foreign T-helper epitope is to be introduced. The introduction of a T-helper epitope according to

2002/009037A1 must be made so as to essentially preserve tertiary structure of the unmodified protein or at least to preserve B-cell epitopes. No consideration is given to preservation of CTL epitopes and consequently a protein antigen might lose very important CTL epitopes as a consequence of using the modifications set strategies set forth in the reference.

The second reference, Fendly et al., relates to breaking tolerance against HER-2 by using a strong immunologic adjuvant and thereby inducing both humoral and cellular immunologic responses. The only thing that Fendly et al. provides is a teaching that 1) it is desirable to immunize against HER2 to induce immunity and that 2) this can be done by using a strong immunological adjuvant.

The mechanisms involved when using a strong immunological adjuvant, however, have nothing to do with the mechanisms that rely on introduction of foreign T-helper epitope. The first approach somehow activates CTLs or induces immunity towards autologous T-helper epitopes. The latter approach, on the other hand, relies on recognition by T-helper cells of the foreign T-helper epitope. As a consequence, the skilled person would not be motivated to arrive at the invention claimed in amended claim 67 by combining the primary reference with Fendly et al. In particular, the claimed invention involves the essential feature of preservation of CTL epitopes in the HER-2 analogue. Since this feature is neither taught nor suggested in the primary reference, the skilled person would not turn to this reference in order to prepare an alternative to the Fendly et al. technology. This is especially true because introduction of foreign T-helper epitopes cannot be considered "immunorestoration."

Indeed, the primary reference does not teach that it would be possible to invoke a cellular immune response against a self-protein by immunizing with an analogue that includes foreign T-cell epitopes. This finding, however, is the basis of the presently claimed invention. That is, that induction of effective CTL immunity that targets self-proteins can be accomplished by providing a T-helper cell response which recognizes a foreign T-helper epitope in the modified self protein.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claims 93 and 94 as obvious over US 2002/0090379A1 in view of Fendly et al. as discussed above and further in view of A_Geneseq_101002 Accession No. AAR06310 or AAW11505 or EP37881A or WO9640789A and AAR11896 or EP427347A.

The Examiner contentions regarding US 2002/0090379A1 and Fendly et al. are discussed above. The Examiner acknowledges that the combined references do not teach the natural T_H epitope having SEQ ID NO. 12 or SEQ ID NO. 14. The remaining references teach these two sequences.

The Examiner contends that it would have been obvious to the skilled artisan to make analogues of the Her2 protein taught by the combined references and using the universal T_H epitope consisting of the sequence of SEQ ID NO. 12 or No. 14 using one of the remaining references. She contends that one would have been motivated to do this in order to treat human adenocarcinomas as taught by the combined references in a variety of persons with diverse HLA haplo types by using a "universal" T_H epitope as taught by the new references cited. Applicants respectfully traverse.

Applicants refer to the discussion of the 2002/0090379A1 and Fendly et al. references as set forth above. Since these two references do not make the instant invention obvious, the mere disclosure of the particular amino acid sequence used as the T-helper epitope does not fill the void and make the instant invention obvious. As a consequence, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claims 67 and 68 as obvious over WO 95/05849 in view of Fendly et al. The Examiner contends that WO 95/05849 teaches analogues of self-proteins that are made immunogenic by inserting foreign T_H cell epitopes, including those from tetanus, and that such analogues may be used to treat cancer. The Examiner acknowledges that this reference does not teach the particular analogues having the self-protein of human Her2.

The Examiner's discussion of the Fendly et al. reference is noted above.

The Examiner contends that it would have been to the skilled artisan to have made analogues of the Her2 protein taught by Fendly et al. with inserted foreign T_H cell epitopes as taught for the self-protein analogues of WO 95/05849 and to have

administered it with the adjuvant taught by Fendly et al. She contends that the motivation to do this would come from the desire to treat human adenocarcinomas as taught by Fendly et al. by directing the patient own immune system toward these tumor cells that over express Her2 as taught for the self-proteins of WO 95/05849. Applicants respectfully traverse.

Like the reference 2002/009037A1, WO 95/05849 deals with induction of antibodies that are reactive with self-proteins – nothing is mentioned about the possibility of inducing anti-self cellular immunity. Again, the aim of the WO 95/05849 reference is first and foremost to preserve B-cell epitopes. As discussed above, this objective is not necessarily compatible with the aim of preserving CTL epitopes. Since no consideration is given to preserving CTL epitopes, a protein antigen could lose very important CTL epitopes as a consequence of using the modification strategies set forth in the reference.

Again, the Fendly et al. reference does not cure this void. As a consequence, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claims 84, 85, 87, 88, 90, 91, 93 and 94 as obvious over WO 95/05849 in view of Fendly et al. as discussed above and further in view of A_Geneseq_101002 Accession No. AAR06310 or AAW11505 or EP37881A or WO9640789A and AAR11896 or EP427347A.

The Examiner's discussion of WO 95/05849 and Fendly et al. are discussed above. The Examiner acknowledges that the combined references do not teach the natural T_H epitope as being promiscuous and having the sequence of SEQ ID NO. 12 or SEQ ID NO. 14.

The Examiner's discussion regarding A_Geneseq_101002 Accession No. AAR06310 or AAW11505 or EP37881A or WO9640789A and AAR11896 or EP427347A is also set forth above.

The Examiner concludes that it would have been obvious to the skilled artisan to have made analogues of the HER2 protein taught by the combined references and using the universal T_H epitope consisting of SEQ ID NO. 12 or SEQ ID NO. 14 as taught by the new reference sited. She contends that one would have been motivated to do this in order to treat human adenocarcinomas as taught by the combined references

and a variety of persons with diverse HLA haplotypes by using a "universal" T_H epitope as taught by the new references cited. Applicants respectfully traverse.

Applicants refer to the discussion of the WO 95/05849 and Fendly et al. references as set forth above. Since these two references do not make the instant invention obvious, the mere disclosure of the particular amino acid sequence used as the T-helper epitope does not fill the void and make the instant invention obvious. As a consequence, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claims 67 and 68 as being obvious over Dalum et al. in view of Fendly et al. The Examiner contends that Dalum et al. teach breaking of B cell tolerance towards a self-protein using a foreign T_H cell epitope inserted into the protein. She further contends that Dalum et al. teach that the T cell response was to the inserted epitope as well as to neo epitope formed by a combination of the inserted epitope and part of the neighboring self-protein. Dalum et al. teach treatment of diseases by induction of autoantibodies. The Examiner acknowledges that Dalum et al do not teach the self-protein human HER2.

The Examiner's discussion of Fendly et al. is as set forth above.

The Examiner contends that it would have been obvious to the skilled artisan to have made analogues of the HER2 protein taught by Fendly et al. with inserted foreign T_H cell epitopes has taught for the self protein analogues of Dalum et al. She contends that one would have been motivated to do this in order to treat human adenocarcinomas as taught by Fendly et al. by directing the patients own immune system toward those tumor cells that over express Her2. Applicants respectfully traverse.

As discussed above for 2002/009037A1 and WO 95/05849, this reference deals with induction of antibodies that are reactive with self-protein. Once more, nothing is mentioned about the possibility of inducing anti-self cellular immunity. As a consequence, the arguments presented above for the 2002/009037A1 and WO 95/05849 references are also applicable here. That is, the combination of references do not teach that it would possible to invoke a cellular immune response against a self-protein by immunizing with an analogue that includes foreign T_H cell epitopes. As a

consequence, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner rejects claims 84, 85, 87, 88, 90, 91, 93 and 94 as being obvious over Dalum et al. in view of Fendly et al. as applied to claim 67 and 68 above and in view of A_Geneseq_101002 Accession No. AAR06310 or AAW11505 or EP37881A or WO9640789A and AAR11896 or EP427347A.

The Examiner's discussion of Dalum et al. and Fendly et al. is set forth above. The Examiner acknowledges that these combined references do not teach the natural T_H epitope as being promiscuous and having the sequence of SEQ ID NO. 12 or SEQ ID No. 14.

The Examiner's discussion of A_Geneseq_101002 Accession No. AAR06310 or AAW11505 or EP37881A or WO9640789A and AAR11896 or EP427347A is also set forth above.

The Examiner contends that it would have been obvious to the skilled artisan to make analogues of the Her2 protein taught by the combined references and using the "universal" T_H epitope consisting of the sequences of SEQ ID NO. 12 or SEQ ID NO. 14 as taught by A_Geneseq_101002 Accession No. AAR06310 or AAW11505 or EP37881A or WO9640789A and AAR11896 or EP427347A. She contends that one would have been motivated to do this in order to treat human adenocarcinomas as taught by the combined references and a variety of persons with diverse HLA haplo types by using a "universal" T_H epitope as taught by A_Geneseq_101002 Accession No. AAR06310 or AAW11505 or EP37881A or WO9640789A and AAR11896 or EP427347A. Applicants respectfully traverse.

Applicants discuss the Dalum et al. and the Fendly et al. references above. Since the combination of these two reference do not teach or suggest that it is possible to invoke a cellular immune response against a self-protein by immunizing with an analogue that includes foreign T_H cell epitopes, these new references, taken alone or in combination, do not cure that void. As a consequence, Applicants respectfully request reconsideration and removal of the rejections.

Allowable Claims

The Examiner has indicated that claims 69, 86, 89, 92 and 95 would be allowable if re-written in independent form including all of the limitations of the base claim and any intervening claims. Applicants note that claims 69 has been amended to be an independent claim and now has all of the limitations of the base claim and intervening claims. Claims 86, 89, 92 and 95 are dependent on claim 69 and so these are now allowable as well.

In view of the above remarks, all of the claims remaining in the case are submitted as defining non-obvious, patentable subject matter.

Conclusion

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), the Applicant respectfully petitions for a one (1) month extension of time for filing a response in connection with the present application and the required fee of $110.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Certificate of Transmission
I hereby Certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office:
On May 3, 2004
Date
Sandra B. Paulo
Signature
SANDRA B. PAULO
Typed or printed name of person signing certificate

Respectfully submitted,
BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____ #47,604
for Leonard R. Svensson, #30,330
P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

LRS/SWG/sbp
4614-0107P